NIH Center for Scientific Review

peer review notes

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In this Issue

How Will NIH's New Application Resubmission Policy Affect Reviewers?

NIH responded to a mountain of applicant requests by eliminating its "two-strikes-and-you're-out" policy that allowed researchers only one resubmission if their initial grant application was unsuccessful. Tight budgets turned a policy that was meant to cut the wait-time for funding into a barrier that prevented further review and funding of valuable research.

Dr. Sally Rockey Director of the NIH Office of Extramural Research explained the new policy, "We will still allow a single resubmission per application, so if you would like, you can resubmit if your initial application was unsuccessful and comment on the previous review. But now ideas that were unsuccessfully submitted [as an A0 or A1 application] may be presented in a new grant application without a substantial redesign in content and scope of the project."

Will Reviewers and CSR Be Overwhelmed by More Applications?

"Of course, we're concerned an increase in applications will be a burden," said CSR Director Dr. Richard Nakamura. "Fortunately, the upcoming round typically sees 10

percent fewer applications than the others, so we'll have a significant buffer and get an early alert on what to expect next. Armed with this knowledge, we'll know if we need to hire more staff or work with NIH to consider options for reducing reviewer burdens."

Modeling done by the NIH Office of Extramural Research suggests the increase in applications will be less than many fear. "Most applicants submit one application at a time to NIH," said Dr. Rockey, "and we believe -- after an up-tick –- this will be the case in the long-term."

What Should Reviewers Look Out For?

Since applicants will be submitting "new" (A0) applications based on earlier unsuccessful applications, reviewers will need to be mindful of a few things:

- If you have seen an A0 application before, review it as if it were new.
- If you think an application has fundamental shortcomings and could never be competitive, it is okay to use the Additional Comments to Applicant box to say as much.

We will give further guidance later as we sort through the issues that could crop up in the application and review processes.

Being Hopeful but Vigilant

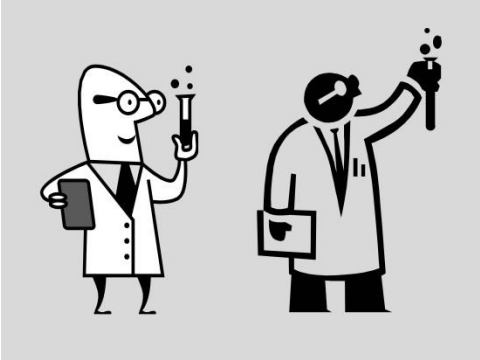
"We all hope the policy change will benefit the community and give life to valuable research that was hindered by the old policy," said Dr. Nakamura. "But like any big change, we need to monitor the results and seek feedback from our reviewers and SROs. Beyond looking at numbers and success rates, we'll monitor application queuing and award delays as well as keep track of how many applications come in that are very similar to earlier submissions."

Get More Information

- Read the Frequently Asked Questions on this new policy
- Follow the discussion on the Rock Talk Blog

Enhancing Reproducibility and Rigor of Research Findings

By Dr. Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH



The "Here and Now"

Publications in both the scientific and lay presses have focused on the reproducibility and transparency of research findings. In October 2013, the Economist devoted two separate articles to the issue, and you do not have to look far to find examples in scientific journals that raise concerns about rigor in all areas of research, both clinical and preclinical.

NIH has focused on the preclinical side of the issue. Earlier this year in January, NIH Director Francis Collins and I wrote a commentary in Nature, discussing NIH efforts to address reproducibility. And more recently, the Director of the NIH Office of Research on Women's Health Dr. Janine Clayton and Dr. Collins published new policies to ensure that NIH preclinical research considers females and males.

The Landscape

As pointed out in both our Nature commentary and numerous other articles on reproducibility, science has the reputation of being "self-correcting." Science depends on the reproduction or replication of previous work, and therefore, is thought to be protected against issues of irreproducibility. In the long-term, this remains true. Over the short- and medium-term, however, those checks and balances that work well in the long-term are hobbled by multiple factors, resulting in the compromised ability to reproduce the findings of others.

The most common association made with regard to irreproducibility is with scientific misconduct, which is defined as falsification, fabrication, or plagiarism. Let me be clear: Misconduct is one of the potential causes of problems with reproducibility, but it represents a small fraction. In 2011, the Office of Research Integrity (part of the U.S. Department of Health and Human Services) found only 12 credible cases out of the 240 allegations of scientific misconduct it received.

There is a complex array of other factors driving the current concerns about the rigor of research findings. Such factors include poor training of researchers in experimental design, which often leads to fundamental characteristics of a study not being reported or performed, e.g., blinding, randomization, sample size calculations. Another factor is the emphasis on what can be considered "cartoon biology," a focus on the potential big picture finding that overshadows the need to include important experimental details.

The difficulty in publishing negative or inconclusive findings also contributes to irreproducibility. Take a hypothetical example, in which an experiment is done 19

different times by 19 different labs, all with negative results. The 20th repeat by a different lab "works," and gets published, despite what could be learned from the previous 19 attempts. Studies that point out flaws in previously published work are hard to get published as well, further compounding the problem and robbing the scientific community of valuable information.

The aforementioned issues also hint at yet another concern, which runs throughout the ones previously mentioned: the reward culture in the biomedical research enterprise. Incentives to publish (and in "high-impact" journals) can be found everywhere, and often do not facilitate investigators having neither the time nor the support to thoroughly consider their work without prioritizing the importance of having that work be attractive for publication. When one's publication record influences everything from grant and institutional support to tenure and promotion decisions to potential cash rewards for publishing, incentives to publish that were intended to be beneficial can become quite perverse.

NIH Scope and Efforts

As previously mentioned, preclinical research, especially work using animal models, seems to be most susceptible to concerns and problems with rigor and transparency of research findings. Current NIH efforts to address some of the potential issues in this area include:

- Development of a training module on enhancing reproducibility with an emphasis on experimental design that will be piloted with NIH intramural postdoctoral fellows later this year, and provided to the extramural community online in its final form.
- Pilots within the NIH Institutes and Centers (ICs) to:
    - Evaluate the "scientific premise" of grant applications
    - Develop and use a checklist to ensure more systematic evaluation of grant applications
    - Reduce "perverse incentives" by examining and exploring options such as making changes to the NIH biosketch requirements and providing longer-term support for investigators
    - Support replication studies, in the case of preclinical studies that are being considered for translation into clinical trials.

NIH leadership will use the information gained from the pilots to decide which approaches could be implemented NIH-wide, which would be best kept at the Institute/Center-level, and which should be eliminated altogether. In addition, NIH ICs continue to support existing efforts and explore others to improve rigor in research, such as:

- The National Institute of Neurological Disorders and Stroke continues to play a leading role in reproducibility and rigor-focused efforts, including the formation of a Scientific Rigor Working Group and issuing guidance to applicants and reviewers to increase the awareness of the importance of transparent reporting and rigorous study design.

- The National Institute on Aging supports an Interventions Testing Program, in which preclinical studies are conducted with multi-site duplication, rigorous methodology and statistical analysis.
- The PubMed Commons was launched in December 2013 as a forum for open discourse about published articles.
- The National Institute of General Medical Sciences is working to facilitate and promote the development of consensus standards for cell line authentication and tools for cell line characterization.

That's Great, But…

These examples, while encouraging and beneficial, highlight the truth emphasized in the January Nature commentary: NIH efforts alone will not be sufficient to address the issue of reproducibility. To that end, we continue to engage with stakeholders in the research community, including journal editors, the pharmaceutical industry, academic research institutions, professional societies, and research reagent suppliers. Of course, our conversations with stakeholders are not the only channel for discussions on reproducibility, but we hope they are an additional catalyst for other sectors of the research enterprise to have conversations about how this issue can be addressed.

We at NIH continue our focus on making systematic changes that should reduce the severity and frequency of this problem, but broader success is dependent upon the commitment of the full research enterprise.

New Efforts to Maximize Fairness in NIH Peer Review

CSR invites you to submit your ideas for identifying and addressing the sources of possible bias in peer review for two new American Competes Act Challenges. Learn about this and many other efforts to maximize fairness in NIH peer review by going to the NIH Rock Talk blog. CSR Director Dr. Richard Nakamura is a guest blogger this month.

Maintaining Confidentiality in NIH Peer Review

"I'm often impressed and stirred when I go to a peer review meeting," said CSR Director Dr. Richard Nakamura. "Discussions are usually powered by an amazing, high-octane mix of scientific rigor and conscientiousness."

"We thus find it hard to imagine anyone breaking the confidentiality rules and laws they pledged to obey. But it sometimes happens," he said.

A couple of recent violations have moved NIH to post an NIH Guide Notice to remind reviewers and applicants how important these rules and laws are.

"There's no big crime wave here," said Dr. Nakamura. "We've become more conscious of the risks of breaking confidentiality. Even if one reviewer acts out of what seems like good intentions, the door is opened to harming applicants and the scientific process, which can only thrive in a culture where the ideas and confidentiality of other scientists are protected."

Some Specific Things You May Not Do

- ***Share an application with a colleague, supervisor, lab member, fellow, or student.*** If you feel such a person could be an asset to the review of a specific application, ask your Scientific Review Officer.

- ***Let anyone use your account to access the secure NIH systems used to facilitate the review of NIH grant applications.***

- ***Discuss in any way information about the review deliberations, evaluations or related documents with anyone not authorized to participate in the review process.*** If an applicant or anyone else attempts to discuss a review with you, please let him know that he should talk with the SRO or their program officer. You also should let your SRO know.

More Things You Should Know

There are other violations to note and we encourage scientists to learn more. To do this, check out the recent NIH Guide Notice and the Confidentiality in Peer Review Web page.

Update on the New NIH Biosketch Format

To help applicants and reviewers better focus on the applicant's most important contributions to science, NIH is working on a new biosketch format. NIH recently launched a new round of pilot tests (here and here) to make sure the new format will work well for both applicants and reviewers.

The new format will allow up to five pages for the entire biosketch. Rather than simply listing publications, the new format will give researchers the opportunity to highlight the magnitude and significance of the scientific advances associated with their discoveries and the specific role they played in those findings. At the same time, it should give reviewers a clearer picture of a researcher's accomplishments and capabilities.

Researchers will be permitted to describe up to five of their most significant contributions to science, the influence of those contributions on their scientific field, and any subsequent effects on health or technology. The new format also will allow researchers to describe their specific role in those discoveries and to annotate their description with up to four publications. In addition, researchers will be able to include a link to their complete list of publications in SciENcv or My Bibliography.

The pilot will involve surveys of both reviewers and applicants to help NIH fine-tune the application instructions and guidance to reviewers. NIH plans to roll out the modified biosketch for all grant applications received for FY 2016 funding and beyond (which generally refers to applications submitted in early 2015).

Power of Peer Review: Basic Research in Yeast May Yield New Approach to Treating Cancer

Since the 1930s, scientists knew that calorie restriction could extend lifespans. But it is only in recent years that the tools were available to discover how this happens.

In 2002, a new investigator at the University of Southern California—Davis School of Gerontology, Dr. Valter Longo, submitted an R01 application to study the mechanisms of longevity regulation in yeast. He proposed to elucidate the molecular pathways that "promote reproduction in response to glucose/nutrients, activate multiple stress resistance systems and extend the life span of non-dividing yeast" in low-nutrient states.

Armed with this information, one could then modulate one of the pathways to "increase resistance to damage and extend longevity in organisms ranging from

yeast to mammals by shifting the investment of energy from growth and reproduction to multiple stress resistance systems."

It was an ambitious application that impressed CSR reviewers. "[It] breaks significant new ground by developing a new model system for studying chronological aging," said one reviewer who was quoted in the summary statement. "The proposal is strongly hypothesis driven, and closely argued throughout. A wealth of preliminary data is presented."

The National Institute on Aging (NIA) was also impressed and funded the grant. "This was exciting research," said Dr. Felipe Sierra recently, speaking on behalf of NIA as its Director of the Division of Aging Biology. "It wasn't translational research at all," he noted. "But by understanding these mechanisms in depth, there was the chance of getting something useful." No one, however, probably imagined how much would come from this research.

Dr. Longo achieved his aims and then some. He identified the Tor-S6K and Ras-PKA pathways as central promoters of aging, and showed how restricted diets lengthened lifespans by decreasing their activity. The role of these pathways in aging was later confirmed in multiple organisms, including mice. He was able to get his yeast cells to live 10 times longer. His research then opened up a whole new approach to fighting cancer.

The Leap into Cancer Research

Dr. Longo knew the genes that mutate and give rise to cancer were the same genes that block protection and promote aging. The genes are always on in cancer cells to help maximize growth. Thinking about how normal and cancer cells evolved, he hypothesized that cancer cells might respond differently if "starved." "Normal cells know what to do because they have seen it throughout evolution," he said. "But cancer cells have gained mutations that make them very good in normal, high nutrition environments but unresponsive to the starvation signal to go into a protected anti-aging mode, and unable to survive well in a starvation environment in which glucose and many other nutrients are scarce."

Dr. Longo and his colleagues conducted a series of studies in yeast, mouse and human cells and found that starved normal cells could survive otherwise lethal doses of chemotherapy and starved cancer cells could not thrive and were more susceptible to chemotherapy. They called these effects Differential Stress Resistance and Differential Stress Sensitization.

The next step was to try it in humans, but this wasn't an easy one. "He had a lot of opposition from physicians," said Dr. Sierra. "Putting cancer patients on a fasting diet was counter-intuitive because, when you're on chemo, you lose your appetite, you don't eat and of course that weakens you."

Dr. Longo went back into the lab with his mice, which also suffer weight loss on chemotherapy. The calorie restricted mice on chemo lost weight like the control group, but they recovered much faster than the controls.

Clinicians at USC Norris Cancer Center, the Mayo Clinic and in Europe are now collaborating with Dr. Longo. After a small clinical trial produced promising results, a larger one was initiated and is ongoing. In addition, the National Cancer Institute is funding small business research to develop a nutritional regimen and products for cancer patients on chemo that would be as good as fasting.

"The results are very exciting," said Dr. Sierra. "I don't know if they will pan out in the larger trial. But if they do, it will be a major breakthrough." In any event, countless avenues for aging and cancer research are now open for exploration. It should be no surprise that Dr. Longo is now a professor at the USC Davis School of Gerontology and the Director of the USC Longevity Institute.

The Power of Peer Review

"All of that came from the NIH-funded yeast research," said a grateful Dr. Longo. Of course, there are others to thank. The CSR reviewers who reviewed his application deserve credit for recognizing the potential in it. But this isn't something Dr. Longo seems to have forgotten. Despite all it has taken to keep up with the robust flow of his research and academic responsibilities, he has made time to review NIH grant applications four times over the last five years.

Why Tell This Story?

CSR launched this series of stories in January 2014 to highlight how NIH peer reviewed science powers science and health. "Scientific and health breakthroughs are heralded in the press almost every day," said CSR Director Dr. Richard Nakamura. "And you often can trace them back—directly or indirectly—to one or more NIH peer review groups that found great promise in an application. There are powerful stories that need to be told. They illustrate why support for peer-reviewed science is so important to our future."

Let us know if you have a story you would like us to share about how peer reviewers identified research that had a big impact.

How Can I Become a CSR Reviewer?

We've got the answer if you want to step up your career or if you want to do your part to help the best science flourish in the years ahead. Becoming a CSR reviewer can be a rewarding experience.

But don't take our word for it. See the top seven reasons reviewers give for doing it. It's also worth noting that 85% of the NIH grantees who won Nobel Prizes between 2000 and 2013 were CSR/NIH reviewers.

Contact a CSR Scientific Review Officer

Send your CV to the CSR Scientific Review Officer who oversees a review group that might use your expertise. Find an appropriate review group or study section by going to our Review Group Descriptions Web site. Each study section description page has a link to a roster, which includes a link to the Scientific Review Officer.

Scientific societies and research institutions also may submit names of volunteers.

Who Is Qualified to Review for CSR?

CSR reviewers usually—

- Have substantial and broad independent research experience
- Have received major peer-reviewed grants (R01 or equivalent)
- Understand the review process
- Are dedicated to high quality, fair reviews

If you're an emerging researcher, you should consider applying for our Early Career Reviewer Program. It may help jumpstart your career.

Learn More by Visiting Our Become a Reviewer webpage.

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